General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of selective serotonin reuptake inhibitors.

Bibliographic Source(s)

Hicks JK, Bishop JR, Sangkuhl K, MÃ¼ller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015 Aug;98(2):127-34. [36 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

Clinical laboratories usually test for the more frequently observed cytochrome P450 (CYP) D6 (*CYP2D6*) and *CYP2C19* genetic variants and translate the results into star-allele (*) nomenclature. Each star-allele, or haplotype, is deï¬ned by a speciï¬c combination of single- nucleotide polymorphisms and/or other genetic variants within the *CYP2D6* or *CYP2C19* gene locus. Supplemental Tables S2 and S5 (see the "Availability of Companion Documents" field) provide a list of *CYP2D6* and *CYP2C19* alleles and their functional status. Genetic test results are reported as the summary of inherited maternal and paternal star-alleles referred to as a diplotype (e.g., *CYP2D6*1/*2* and *CYP2C19*1/*1*). The Supplemental Data (Genetic Test Interpretation Section) (see the "Availability of Companion Documents" field) contains additional information regarding *CYP2D6* and *CYP2C19* genetic test interpretation and phenotype assignment.

Different clinical laboratories may use varying methods to predict phenotype from genotype data. Therefore, before any pharmacotherapy modiï¬cations are made based on this guideline, it is advisable to predict a patient's phenotype from genotype as described above and in the Supplemental Data.

Table 1. Assignment of Likely Phenotypes Based on Diplotypes

Table 1a. Assignment of CYP2D6 Predicted Phenotypes			
Likely Phenotype	Activity Score	Genotypes	Examples of *CYP2D6* Diplotypes
Ultrarapid metabolizer (~1%–2% of patients)[a]	>2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[b]
Extensive metabolizer (~77%–92% of patients)	2.0-1.0[c]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41*
Intermediate metabolizer (~2%–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10, *4/*41, *5/*9*
Poor metabolizers (~5%–10% of patients)	0	An individual carrying only no functional alleles	**3/*4, *4/*4, *5/*5, *5/*6*

Table 1b. Assignment of CYP2C19 Predicted Phenotypes		
Likely Phenotype	Genotypes	Examples of *CYP2C19* Diplotypes
Ultrarapid metabolizer (~5%–30% of patients)[d]	An individual carrying two increased function alleles or one normal function allele and one increased function allele	**17/*17, *1/*17*
Extensive metabolizer (~35%–50% of patients)	An individual carrying two normal function alleles	**1/*1*
Intermediate metabolizer (~18%–45% of patients)	An individual carrying one normal function allele or one increased function allele and one no function allele	**1/*2, *1/*3, *2/*17*[e]
Poor metabolizer (~2%–15% of patients)	An individual carrying two no function alleles	**2/*2, *2/*3, *3/*3*

[a]CYP2D6 metabolizer status frequencies are based on data from Caucasians and may differ from other ethnicities. See Supplemental Tables S3 and S6 note for information on the chances of observing specific diplotypes in different major race/ethnic groups.

[b]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see Supplemental Data for additional information on how to translate diplotypes into phenotypes.

[c]Patients with an activity score of 1.0 may be classiﬁed as intermediate metabolizers by some reference laboratories.

[d]CYP2C19 metabolizer status frequencies are based on average multiethnic frequency.

[e]The predicted metabolizer phenotype for the **2/*17* diplotypes is a provisional classiﬁcation. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the no function *CYP 2C19*2* allele. See Supplemental Materials for a more comprehensive list of predicted metabolizer phenotypes.

Therapeutic Recommendations

The recommendations below and in Tables 2 and 3 below apply primarily to actions based on genetic tests only; drug interactions and other clinical factors can have a major inﬂuence for prescribing decisions for selective serotonin reuptake inhibitors (SSRIs) and should be taken into consideration before initiating drug therapy. Based on the current literature, recommendations are made for paroxetine, ﬂuvoxamine, citalopram, escitalopram, and sertraline. Considerations regarding ﬂuoxetine are discussed below and can be found in the Supplemental Material.

CYP2D6-Paroxetine and Fluvoxamine Dosing Recommendations

Table 2 summarizes the dosing recommendations for paroxetine (Table 2a) and ﬂuvoxamine (Table 2b) based on CYP2D6 phenotype. Multiple studies have demonstrated that CYP2D6 ultra-rapid metabolizers have low or undetectable paroxetine plasma concentrations when compared to CYP2D6 extensive metabolizers. Those with undetectable paroxetine plasma concentrations are likely at risk of therapeutic failure. Low paroxetine plasma concentrations may be a risk factor for therapy failure, although the minimal paroxetine therapeutic concentration is not well deﬁned. Because of the risk for therapy failure due to lower drug exposure, an alternative SSRI not extensively metabolized by CYP2D6 should be considered. There are insufficient data to calculate an initial paroxetine dose for CYP2D6 ultrarapid metabolizers. Data are lacking describing the effect of CYP2D6 ultrarapid metabolism on ﬂuvoxamine therapy; therefore, no dosing recommendations are provided for ﬂuvoxamine in the context of CYP2D6 ultrarapid metabolizers. It may be reasonable, though, to select an alternative SSRI not extensively metabolized by CYP2D6 due to the lack of data describing how CYP2D6 ultrarapid metabolizer status inﬂuences ﬂuvoxamine therapy.

Adjustments to paroxetine or ﬂuvoxamine therapy are not warranted based on CYP2D6 status for those who are CYP2D6 extensive or intermediate metabolizers. Self-inhibition of CYP2D6, and potential phenoconversion, may lead to nonlinear kinetics at common doses in certain genotypes. Although CYP2D6 intermediate metabolizers may be expected to have a modest increase in drug exposure and may be more susceptible to CYP2D6 inhibition by paroxetine, existing evidence does not support paroxetine or ﬂuvoxamine therapy adjustments. In addition, because *CYP2D6* diplotypes are inconsistently categorized as extensive or intermediate metabolizers, the literature is difficult to evaluate, thus resulting in a moderate recommendation classiﬁcation for intermediate metabolizers.

When administered similar doses, CYP2D6 poor metabolizers have signiﬁcantly greater drug exposure to paroxetine and ﬂuvoxamine when compared to extensive metabolizers. This increase in drug exposure may be a risk factor for drug-induced side effects. The U.S. Food and Drug Administration (FDA) states that ﬂuvoxamine should be used cautiously in patients known to have reduced levels of CYP2D6 activity (http://www.pharmgkb.org/label/PA166104854). To potentially prevent an adverse effect, an alternative SSRI not extensively metabolized by CYP2D6 should be considered for poor metabolizers. If paroxetine or ﬂuvoxamine is warranted, dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 50% dose reduction of paroxetine and a 30% dose reduction of ﬂuvoxamine. However, a 30% decrease in ﬂuvoxamine dose may not be feasible given the dosage forms; therefore, decreasing the dose of ﬂuvoxamine by 25% to 50% may help prevent adverse events by limiting high drug exposures. Because therapeutic drug monitoring is not common for SSRIs, limited data are available describing the linearity of the dose–concentration relationship and the relation between paroxetine or ﬂuvoxamine concentrations and therapeutic effect and tolerability. Therefore, this recommendation is considered optional.

Table 2. Dosing Recommendations for CYP2D6 and SSRIs

Table 2a. Dosing Recommendation for Paroxetine Based on CYP2D6 Phenotype

Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation
CYP2D6 ultrarapid metabolizer	Increased metabolism to less active compounds when compared to extensive metabolizers. Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure.	Select alternative drug not predominantly metabolized by CYP2D6.[a]	Strong
CYP2D6	Normal metabolism	Initiate therapy with recommended starting dose.	Strong

Table 2a. Dosing Recommendation for Paroxetine Based on CYP2D6 Phenotype			
Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation
CYP2D6 intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate
CYP2D6 poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Select alternative drug not predominantly metabolized by CYP2D6[a] or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Optional

Table 2b. Dosing Recommendation for Fluvoxamine Based on CYP2D6 Phenotype			
Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation
CYP2D6 ultrarapid metabolizer	No data available for CYP2D6 ultrarapid metabolizers.	No recommendation due to lack of evidence.[b]	Optional
CYP2D6 extensive metabolizer	Normal metabolism.	Initiate therapy with recommended starting dose.	Strong
CYP2D6 intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate
CYP2D6 poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 25%–50% reduction[c] of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6.[a]	Optional

[a]Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

[b]Data are lacking describing the effect of CYP2D6 ultrarapid metabolism on ï¬‚uvoxamine therapy; therefore, no dosing recommendations are provided for ï¬‚uvoxamine use for CYP2D6 ultrarapid metabolizers. It may be reasonable, though, to select an alternative SSRI not extensively metabolized by CYP2D6 due to the lack of data describing how CYP2D6 ultrarapid metabolizer status inï¬‚uences ï¬‚uvoxamine therapy.

[c]Dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 30% dose reduction of ï¬‚uvoxamine. However, a 30% decrease in dose may not be feasible given the dosage forms, therefore, decreasing the starting dose of ï¬‚uvoxamine by 25% to 50% should be considered.

Fluoxetine Considerations

CYP2D6 converts ï¬‚uoxetine to S-norï¬‚uoxetine while both CYP2D6 and CYP2C9 convert ï¬‚uoxetine to R-norï¬‚uoxetine (see Supplemental Figure S1). Fluoxetine and R/S-norï¬‚uoxetine modulate serotonin reuptake, although R-norï¬‚uoxetine is thought be less pharmacologically active. CYP2D6 poor metabolizers have been demonstrated to possess signiï¬cantly higher ï¬‚uoxetine plasma concentrations than extensive metabolizers (Supplemental Table S10). However, the total sum of ï¬‚uoxetine plus norï¬‚uoxetine plasma concentrations may not vary signiï¬cantly by CYP2D6 phenotypes. Few data are available describing how CYP2D6 phenotype status inï¬‚uences the total sum of ï¬‚uoxetine plus norï¬‚uoxetine concentrations over time, or if an imbalance between ï¬‚uoxetine and norï¬‚uoxetine concentrations caused by CYP2D6 phenotype status affects patient outcome or safety. Therefore, no gene-based dosing recommendations are provided for ï¬‚uoxetine. For CYP2D6 ultra-rapid and poor metabolizers, it may be reasonable to monitor these patients more closely if they are prescribed ï¬‚uoxetine or to select an alternative SSRI not extensively metabolized by CYP2D6 due to conï¬‚icting/inconclusive data describing how CYP2D6 status inï¬‚uences ï¬‚uoxetine therapy. It is important to note that the prescribing information for ï¬‚uoxetine states that the drug "should be used with

caution in patients with congenital long QT syndrome" and that caution is warranted in situations that may prolong QT such as "conditions that predispose to increased ï¬‚uoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs)."

CYP2C19-Citalopram, Escitalopram, and Sertraline Dosing Recommendations

Table 3 summarizes the dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype. CYP2C19 ultrarapid metabolizers have signiï¬cantly lower exposure to these drugs when compared to extensive metabolizers, and therefore may have an increased probability of failing therapy. Because there are insuffï¬cient data to calculate an initial citalopram or escitalopram dose for CYP2C19 ultrarapid metabolizers, an alternative SSRI not extensively metabolized by CYP2C19 may be an option if deemed appropriate given other medications and clinical considerations. Drug–drug interactions should be considered if selecting an alternative SSRI, such as paroxetine, which inhibits CYP2D6. *CYP2C19*17* homozygotes have a greater metabolic capacity than *CYP2C19*17* heterozygotes, and may beneï¬t more from alternative therapy. Given that there may be clinically signiï¬cant differences among CYP2C19 ultrarapid metabolizers based on diplotype (i.e., *CYP2C19*1/*17* vs. *CYP2C19*17/*17*), this is a moderate recommendation.

Adjustments to citalopram or escitalopram therapy are not warranted based on CYP2C19 status for those who are CYP2C19 extensive metabolizers. Although CYP2C19 intermediate metabolizers may have elevated plasma concentrations, dose extrapolations suggest that minimal dose adjustments are warranted for intermediate metabolizers. Elevated concentrations of these drugs have been observed in poor metabolizers, which may increase the risk of adverse drug reactions. To potentially prevent an adverse effect, an alternative SSRI not extensively metabolized by CYP2C19 should be considered. If citalopram or escitalopram is warranted, an initial dosage decrease of 50% should be considered. For citalopram, the FDA recommends a 50% dose reduction (or a maximum dose of 20 mg/day in adults) for CYP2C19 poor metabolizers due to risk of QT prolongation (the FDA recommendation does not apply to escitalopram). Although limited data are available describing the relationship between SSRI concentrations and therapeutic effect and tolerability, this is a moderate recommendation due to apparent risk of arrhythmias combined with the FDA providing speciï¬c dose recommendations.

Pharmacokinetic data show reduced oral clearance of sertraline in CYP2C19 poor metabolizers but only slightly increased metabolism in ultrarapid metabolizers. Side effects in CYP2C19 poor metabolizers have also been reported to be more frequent than in normal metabolizers. Therefore, in CYP2C19 poor metabolizers a dose reduction of 50% is recommended or an alternative SSRI not extensively metabolized by CYP2C19 should be considered (Table 3 below). No dose adjustment is recommended for CYP2C19 ultrarapid metabolizers; however, if a patient is not responding to adequate maintenance doses of sertraline, consider an alternative SSRI not predominantly metabolized by CYP2C19. Due to the limited available evidence, this recommendation is optional.

Table 3. Dosing Recommendations for CYP2C19 and SSRIs

Table 3a. Dosing Recommendations for Citalopram and Escitalopram Based on CYP2C19 Phenotype

Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation
CYP2C19 ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by CYP2C19.[a]	Moderate
CYP2C19 extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[b,c] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[a]	Moderate

Table 3b. Dosing Recommendations for Sertraline Based on CYP2C19 Phenotype

Table 3a. Dosing Recommendations for Citalopram and Escitalopram Based on CYP2C19 Phenotype

Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation
Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation
CYP2C19 ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.[a]	Optional
CYP2C19 extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[c] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[a]	Optional

[a]Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

[b]Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients greater than 60 years of age.

[c]Percent dose adjustments corresponding to per cent difference in oral clearances have been calculated/estimated by Stingl, et al.

Pediatrics

Data describing the relationship between *CYP2D6* or *CYP2C19* genotype and SSRI systemic exposure or steady-state plasma concentrations in pediatric patients are scarce (see the Supplemental Data). Because CYP2D6 activity is fully mature by early childhood it may be appropriate to extrapolate these recommendations to adolescents or possibly younger children with close monitoring. CYP2C19 activity may be increased in children relative to adults; therefore, these recommendations should be used with caution in children and accompanied by close monitoring. Ultimately, additional research and clinical trials in pediatric patients investigating the association between CYP2D6 or CYP2C19 and SSRI systemic exposure or treatment outcomes is needed.

Recommendations for Incidental Findings

Not applicable.

Definitions

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

The following algorithms are provided in the Supplemental Material (see the "Availability of Companion Documents" field):

- *CYP2D6/CYP2C19* Pharmacogenetic Test Result: Clinical Implementation Workflow for EHR
- *CYP2D6/CYP2C19* Genotype and SSRI: Point of Care Clinical Decision Support

Scope

Disease/Condition(s)

Major depressive disorders, anxiety disorders, and other psychiatric conditions such as obsessive-compulsive disorder

Guideline Category

Evaluation

Prevention

Risk Assessment

Clinical Specialty

Medical Genetics

Pharmacology

Psychiatry

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information to allow the interpretation of existing cytochrome P450 (CYP)2D6 (*CYP2D6*) and/or *CYP2C19* genotype tests to guide selective serotonin reuptake inhibitor (SSRI) dosing, particularly focusing on ï¬‚uvoxamine, paroxetine, citalopram, escitalopram, and sertraline

Target Population

Individuals with major depressive disorders, anxiety disorders, or other psychiatric disorders considering therapy with selective serotonin reuptake inhibitors (SSRIs)

Interventions and Practices Considered

Use of cytochrome P450 (CYP)2D6 (*CYP2D6*) and *CYP2C19* genotyping to guide therapeutic decision-making and dosing of selective serotonin reuptake inhibitors (SSRIs)

Major Outcomes Considered

Effect of cytochrome P450 (CYP)2D6 (*CYP2D6*) or *CYP2C19* on selective serotonin reuptake inhibitor (SSRI) clinical outcomes or effect on SSRI pharmacokinetic parameters

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Review

The authors searched the PubMed® database (1966 to December 2014) for the following keywords: (cytochrome P450 2D6 or CYP2D6) OR (cytochrome P450 2C19 or CYP2C19) AND (SSRI OR selective serotonin reuptake inhibitors OR fluoxetine OR paroxetine OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR paroxetine) for the association between *CYP2D6* and/or *CYP2C19* genotypes and metabolism of SSRIs or SSRI-related adverse drug events or clinical outcomes. Key publications of clinical pharmacogenetic studies on SSRI pharmacokinetics and clinical outcomes are reported in Supplemental Tables S7-S11 (see the "Availability of Companion Documents" field).

The *CYP2D6* and *CYP2C19* allele frequency tables are updates of those previously published in Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. Updates to the *CYP2D6* and *CYP2C19* allele frequency tables were made by searching the PubMed® database (1995 to 2014). The following criteria were used for *CYP2D6*: (CYP2D6 or 2D6 or cytochrome P4502D6) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. The following criteria were used for *CYP2C19*: (CYP2C19 or 2C19 or cytochrome P4502C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2D6* or *CYP2C19* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses).

Number of Source Documents

Using the specified search criteria, 696 publications were identified. Following application of the inclusion criteria and after excluding non-English manuscripts or review articles, 56 publications were reviewed and included in the evidence table.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium's (CPIC's) therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: in vivo pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing cytochrome P450 (CYP)2D6 (CYP2D6) or CYP2C19, in vitro CYP2D6 or CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2D6* or *CYP2C19* genotypes, and in vivo pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

The evidence summarized in Supplemental Tables S7-S11 (see the "Availability of Companion Documents" field) is graded on a scale of high, moderate, and weak, based upon the level of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The gene-based dosing recommendations in this guideline take into consideration the effects *CYP2D6* or *CYP2C19* genetic variants may have on both clinical outcomes and selective serotonin reuptake inhibitors (SSRIs). Because the pharmacokinetic properties of SSRIs do not differ between healthy volunteers and patients, the authors evaluated pharmacokinetic data acquired from studies performed on healthy subjects and patients to assist in determining if *CYP2D6* or *CYP2C19* genetic variants affect SSRIs.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. The Clinical Pharmacogenetics Implementation Consortium (CPIC) uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (see the "Rating Scheme for the Strength of Recommendations"), in which the desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

Clinical variables other than genotype testing that may influence selective serotonin reuptake inhibitors (SSRI) therapy as well as genotyping cost-effectiveness are beyond the scope of this article.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Existing *CYP2D6* and/or *CYP2C19* genotype results may provide the potential beneï¬t of identifying patients who are at an increased risk of experiencing adverse drug reactions or therapeutic failure.

Potential Harms

- The more common adverse effects induced by selective serotonin reuptake inhibitors (SSRIs) include central nervous system effects (e.g., insomnia, headache), gastrointestinal dysfunction, and sexual dysfunction; however, the incidence of side effect occurrence differs with each drug. Serious adverse events such as arrhythmias caused by QT prolongation have been associated with SSRIs, particularly for individuals prescribed citalopram who are cytochrome P450 (CYP) 2C19 (CYP2C19) poor metabolizers.
- When administered similar doses, CYP2D6 poor metabolizers have significantly greater drug exposure to paroxetine and fluvoxamine when compared to extensive metabolizers. This increase in drug exposure may be a risk factor for drug-induced side effects. The U.S. Food and Drug Administration (FDA) states that fluvoxamine should be used cautiously in patients known to have reduced levels of CYP2D6 activity.
- It is important to note that the prescribing information for fluoxetine states that the drug "should be used with caution in patients with congenital long QT syndrome" and that caution is warranted in situations that may prolong QT such as "conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs)."
- FDA product labeling cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients greater than 60 years of age.
- A potential risk is the misinterpretation of genetic test results, as rare or novel variants are typically not interrogated. If an individual carries a rare variant, the actual phenotype may differ from the predicted phenotype. An individual's CYP2D6 and/or CYP2C19 metabolizer status may also depend on other factors including epigenetic phenomena, diet, comorbidities, or comedications. Although *CYP2D6* and/or *CYP2C19* genotyping is usually reliable when performed in qualiï¬ed laboratories, the possibility for error in genotyping, contamination, or mislabeling of the sample remains.

Qualifying Statements

Qualifying Statements

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reï¬,ect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for

further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Patients on a stable and effective dose of a selective serotonin reuptake inhibitor (SSRI) most likely will not benefit from additional dose modifications based on cytochrome P450 (CYP)2D6 (*CYP2D6*) or *CYP2C19* genotype results. Similar to all diagnostic tests, genetic tests are one of several pieces of clinical information that should be considered before initiating drug therapy.

Implementation of the Guideline

Description of Implementation Strategy

The guideline's Supplemental Material (see the "Availability of Companion Documents" field) contains examples of clinical decision support (CDS) tools that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization. Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (Supplemental Tables S12 and S13), workflow diagrams (Supplemental Figures S2 and S3), tables that translate genotype test results into a predicted phenotype (Supplemental Tables S14 and S15), and example text for documentation in the EHR and point-of-care alerts (Supplemental Table S16).

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Bibliographic Source(s)

Hicks JK, Bishop JR, Sangkuhl K, MÃ¼ller DJ, Ji Y, Leckband SG, Leeder JS, Graham RL, Chiulli DL, LLerena A, Skaar TC, Scott SA, Stingl JC, Klein TE, Caudle KE, Gaedigk A, Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015 Aug;98(2):127-34. [36 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

J.R.B. is an advisory board member for Physician's Choice Laboratory Services. S.A.S. is a paid consultant for USDS, Inc., and is an associate director of a clinical laboratory that performs *CYP2D6* and *CYP2C19* genetic testing. A.G. is a paid consultant for Millennium Health, LLC, San Diego, CA. T.E.K. is stockholder in Personalis Inc. All other authors declare no conï¬,icts.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables, methodological information, and implementation resources, is available from the Pharmacogenomics Knowledgebase Web site .
- A cytochrome P450 (CYP)2D6 (CYP2D6) translation table is available from the Pharmacogenomics Knowledgebase Web site .
- A CYP2D6 frequency table is available from the Pharmacogenomics Knowledgebase Web site . The CYP2D6 frequency table legend is also available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

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